Peer Review
Experimental Toxicology Division
N H E E R L

MODELING

Description of ADME of TCDD in Mother and Fetus During Gestation with Physiologically Based Pharmacokinetic Model

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Environmental issue

Dioxins are a group of persistent environmental contaminants which are present in all strata of the environment. Tetrachlorodibenzo-p-dioxin (TCDD) is the most toxic in this group. TCDD induces developmental reproductive, immunological, and neurological toxicities in male and female animals. The windows of sensitivity for these effects in animals appear to be during gestation. Humans are thought to have similar windows of sensitivity. Pharmacokinetic and toxicity studies in our laboratory indicate that fetal TCDD concentrations are good predictors of the developmental reproductive effects of TCDD in rats. Presently, there are no models available to predict human fetal TCDD concentrations. Development of a physiologically based pharmacokinetic (PBPK) model to predict fetal concentrations in humans would provide risk assessors a tool to assess the impact of a variety of exposure scenarios on fetal concentrations of TCDD.

STUDY GOAL

To develop a PBPK model that describes the distribution and elimination of TCDD in women and their fetus during gestation.

Methods

This PBPK model consists of 4 compartments for the dam (liver, fat, rest of the body and placenta) and 1 compartment for the whole fetus (Figure 1). All compartments except the fetus were described as diffusion limited. The PBPK models for TCDD describe the pharmacokinetic properties and Ah receptor-mediated to CYP1A2 induction. All the parameters came from the literature. The simulations were supported by the software ACSL®. The model was validated for naïve female rats with the same data sets used by Wang et al. (1997). After validation, the model was used to simulate gestational or none exposures in rats or mice compared to experimental data obtained from the peer-reviewed literature. Data of Hurst et al from our lab were used for the development and the validation of this model for pregnant animals. We also simulated human exposures with the model and compared the model to data available in the peer-reviewed literature.

Figure1: Conceptual PBPK model representation used to study the developmental distribution of TCDD for rodents and human.

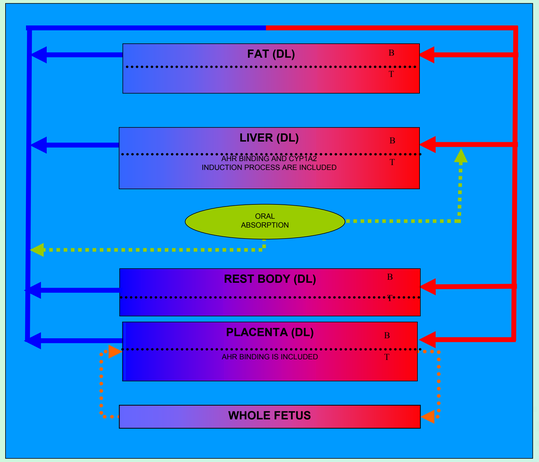


Figure 2: Distribution of TCDD in rat after a single dose (0.05 µg TCDD/kg on GD15 using a fixed elimination rate.

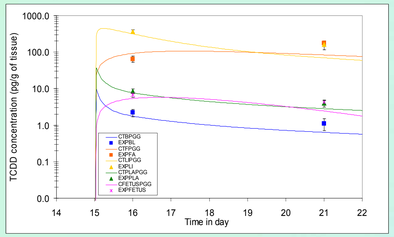


Figure 3 : Distribution of TCDD in rat after a single dose (0.05 µg TCDD/kg on GD15 using a variable elimination rate.

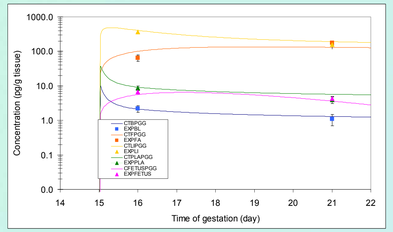


Figure 4: Distribution of TCDD in mice after subchronic exposure to 0.15 µg TCDD/ kg/day/5 day/week for 17 weeks using a fixed elimination rate.

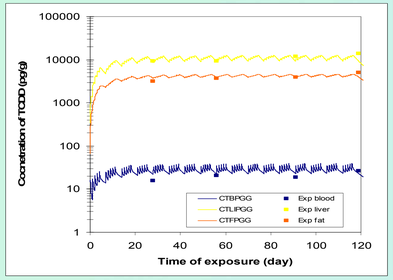


Figure 5: Pharmacokinetic distribution of TCDD in humans after a repetitive oral doses 0.32 pg TCDD/kg/day for 20 years prior to pregnancy using a fixed elimination rate.

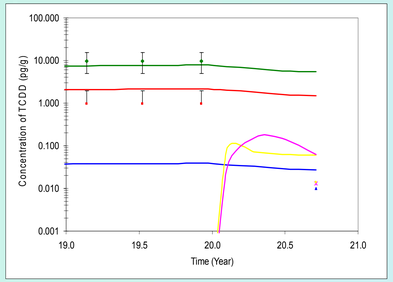
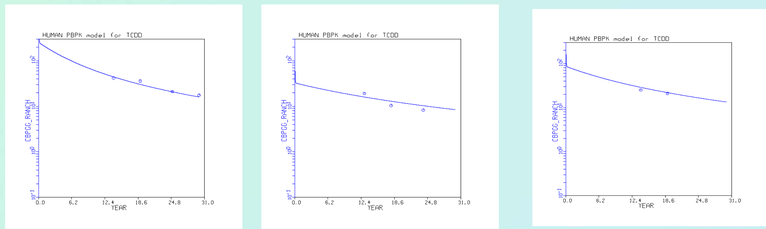


Figure 6: An example of PBPK modeling of blood TCDD concentration data from Veterans of Operation Ranch Hand. A dose dependent elimination rate was used. As dose increases the elimination rate increases.



Results

- Inclusion of a dose dependent elimination rate of TCDD provides a better fit (Figure 3) compared to a fixed elimination rate (Figure 2).
- This model also predicts a subchronic exposure of TCDD in mice (Figure 4).
- An initial simulation of human exposures using with a fixed elimination rate compares well with the epidemiological human data (Figure 5). However a number of assumptions had to be made on the exposure so these results must be viewed cautiously.
- A preliminary simulation of the data from Operation Ranch Hand Veterans has been conducted and predicts well serum TCDD concentrations (lipid adjusted) when a dose dependent elimination rate is used (Figure 6a, b, and c).

Discussion

The model predicts maternal and fetal tissue concentrations from acute and subchronic exposures during in rats. The model was modified to include dose dependent increases in the TCDD elimination rate and the model fits of both the acute and subchronic exposures improved. Experimental data on the distribution of TCDD in pregnant mice is limited. However, the model provided good fits to the experimental data for non-pregnant mice. Initial simulations of human exposures compared reasonably well to the epidemiological data published in the literature. Considering that the exposure dose had to be estimated a comparison among epidemiological data and simulation demonstrated reasonable concordance. However, the inclusion of a variable elimination rate provides a better predictive tool to estimate the elimination of TCDD in rodent and humans.

Future direction

Several new data sets that provide repeated TCDD blood concentrations measurements for the same individuals are now available. These data sets are from Vietnam War Veterans exposed during Operation Ranch Hand and in men and women exposed during the industrial accident in Seveso Italy. We have begun collaborations with these groups and this data will allow us to better refine and validate the human model.

Impact

The development of this PBPK model for humans can provide risk assessors and managers a predictive tool to better understand the relationship between human exposures and target tissue concentrations. This information may better inform risk managers and improve risk management decisions.

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